04-12-07

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(CASE NO. MBHB00-203)

In Re Application of:	)	
	)	
Ruderman, et al	)	**Examiner: Carolyn Bleck**
	)	
Serial No.: 09,534,946	)	
	)	**Group Art Unit: 3626**
Filed: March 24, 2000	)	
	)	
Title: CARDIOVASCULAR HEALTHCARE MANAGEMENT SYSTEM AND METHOD	)	

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In regard to the above identified application:

1. We are transmitting herewith the attached:

2. a. Amended Appeal Brief (in triplicate); and
   b. Postcard.

3. No fee is required.

4. Please charge any additional fees or credit overpayment to Deposit Account No.13-2490.

Respectfully submitted,

McDONNELL BOEHNEN
HULBERT & BERGHOFF

John J. McDonnell
Reg. No. 26,949

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CERTIFICATE OF MAILING UNDER 37 CFR § 1.8: The undersigned hereby certifies that this Transmittal Letter and the papers, as described in paragraph 1 hereinabove, are being deposited with the United States Postal Service with sufficient postage as U.S. Express Mail No.EV839380519US addressed to: Mail Stop Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 11 day of April 2007.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
(CASE NO. MBHB00-203)

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Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

AMENDED APPEAL BRIEF
37 C.F.R. § 1.192(d)

Dear Sir:

This Amended Appeal Brief is submitted pursuant to a Patent Office Notice of Non-Compliant Brief dated March 21, 2007, in Section V, Summary of Claimed subject Matter. The amended Section V is incorporated into the Brief.

I. Real Party in Interest

Berkeley Heartlabs, Inc.
839 Mitten Road
Burlingame, CA 94010-1318

II. Related Appeals and Interferences

None

III. Status of Claims

Independent claim 38 and claims 22-28 dependent thereon are rejected as obvious over the prior art. Claim 38 and claims 22-28 are appealed.

IV. Status of Amendments

None pending

V. Summary of the Claimed Subject Matter (Amended)

Claim 38 is directed to a cardiovascular healthcare management system comprising:

a) a cardiovascular healthcare management system comprising: (a) an infomediary site having databases for cardiovascular healthcare management which includes a database of test results of concentration of subclasses of LDL particles and subclasses of HDL particles from at least 900 cardiovascular patients;

A schematic of the infomediary site is shown in Figure 1 and is described at page 3, lns 25-30 including database 104 also see Fig. 24 which shows a more detailed view of the infomediary site. Figures 18-22 illustrate the database as pointed out at pp. 16, lns 19-25.

Page 14 lns 10-16 refers to data for 954 patients studied. Figures 8 and 15 illustrate HDL and LDL subclass data. Figure 8 is further described at pp. 7, lns 3-27. Figure 23 shows the information in the database for example, block 902 shows LDL and HDL subclasses.

(b) a data entry interface for receiving patient personal data and test results for concentration of subclasses of LDL particles and subclasses of HDL particles storing the data and results in the infomediary site databases;

Figure 1 108 provides for inputting data from lab pp. 4, lns 1-3 with infomediary database 104. Also see Figure 24 which shows infomediary databse 104 and claimed database 105 interacting through the database management system (DBMS). Also see flow chart processing of patient data in Figures 25 and 26.

(c) a diagnostic engine for analyzing patient test results for subclasses of LDL particles, subclasses of HDL particles data and identifying patients who do not have hyperlipidemia based on total LDL cholesterol and total HDL cholesterol, but are in need of treatment;

Figure 24 113 shows diagnostic engine which is referred to on pp 10, ln 29; pp 19, ln 25; pp 18, ln 24-26. Also see pp. 14, lns 28-41 for discussion on patients without hyperlipidemia and elevated HDL 2b. Figures 25 and 26 illustrate flow chart for handling data.

(d) wherein the subclasses of LDL particles and subclasses of HDL particles are levels determined by segmented gradient gel eletrophoresis and wherein the particle sub-classes include HDL 2b.

Page 13, lns 39-55 refers to gradient electrophoresis methods for determining LDL and HDL sub-classes HDL 2b is referred to on pp 7, ln 10, 13 & 19; pp 14, ln 29; pp 15, lns 1 and 2; also see Fig 5 under test data. Figures 8 and 15 illustrate gradient gel electrophoresis data. Figure 23 refers to various LDL and HDL subclasses.

Claim 23
Further comprises a system allowing physicians to communicate with the cardiovascular healthcare information to the patient. See Figure 1 which shows communication between patient and physician 102 (physician) ⇆ 112 ⇆ 106 (patient). Also see Figure 24 107 (patient terminal) 103 (physician terminal) connected to network 101.

Claim 24
Further comprising a cardiovascular knowledge base that stores information related to cardiovascular risk factors. See Figure 23 904 which identifies risk factors referred at pp. 10, ln 26.

Claim 25
Further including algorithm for associating test results with possible treatments. See figure 24 105 (clinical database) and discussion on pp. 11, lns 3-20 where diagnostic engine 113 is discussed with possible treatment 908 of Figure 23. See Figures 25 and 26 to flow diagram to obtain a suggested treatment.

Claim 26
Including algorithms for associating test results with diagnosis. See discussion under claim 25. For example, see Figures 25 and 26 and diagnostic engine 113 and clinical database 105 of Figure 24.

Claim 27
Including algorithms for associating diagnosis information with treatment plan. See Figures 25 and 26 and discussion for claims 25 and 26.

Claim 28
For treatment plans related to personalized drugs, diet, exercise, see Figure 22 and related discussions on pp. 18, lns 27-31 and pp. 19, lns 1-6.

VI. Grounds of Rejection to be Reviewed on Appeal

Claims 38 and 22, 24-28 and 38 are rejected as obvious over U.S. Patent 5,724,580 (Levin); U.S. Patent 6,576,471 (Otvos); and U.S. Patent 5,925,229 (Krauss). The application of the references by the Patent Office is as follows:

Levin discloses a storage means that stores information about test results (col. 5 lines 2-16) in a storage means (see previous Office Action for discussion of this feature. Levin does not expressly disclose the database storing data of at least 900 patients. However, Levin clearly teaches that the pool of patient information stored in the database will grow over time (col. 6 lines 3-15). The Examiner respectfully submits that it is well known in the medical database arts to store data for large numbers of patients. For example, it is well known that large hospitals and even small medical practices have databases storing records for more than 900 patients. It would have been obvious at the time of Applicant's invention to include this feature with the motivation of determining the effectiveness of diagnoses and treatments as information is gathered over time based on large numbers of patients (Levin; col. 6 lines 3-15).

Otvos discloses generating lipoprotein measurement values for a patient's blood sample, the lipoprotein measurement values including a plurality of lipoprotein subclass variable measurements, including LDL size, LDL concentration (reads on "concentration of subclasses of

HDL"), large HDL concentration (reads on "concentration of subclasses of HDL"), large VLDL concentration, LDL-C and HDL-C (see Fig. 2: 71), comparing the plurality of patient lipoprotein subclass variable values with respective predetermined test criteria for determining whether the subclass variable values are associated with a higher or lower risk of developing coronary heart disease, evaluating the lipoprotein measurement values and generating a reduced target value or values for what represents an optimal or low risk value for selected lipoprotein constituents to provide a patient-specific treatment guideline based on the presence of predetermined risk criteria, and automatically generating personalized lipoprotein-based reports for patients (Fig. 1:32, 32a, 33, 33a, 33b, 43, 43a, 43b, Fig. 2, 2A, 3, 4, 5, 7, 8, 9, 11, 14, col. 3 line 32 to col 4 line 5, col. 5 lines 22-45, col. 11 lines 12-46, col. 16 lines 48-62, col. 19 line 55 to col. 20 line 40).

As per the recitation of "identifying patients who do not have hyperlipidemia but are in need to treatment", Otvos teaches using NMR spectroscopy to obtain subclass information, wherein the subclass information is a more reliable indicator of a patient's risk to develop coronary heart disease, wherein various subclasses of lipoproteins may provide more reliable markers of the metabolic conditions that predispose individuals to a greater or lesser risk of heart disease (col. 1 line 42 to col 2 line 11). Further, Otvos teaches that without an NMR subclass profile, a patients with a specific type of lipid profile may have been overlooked as a candidate for further review or potential behaviour altering counseling (or even drug therapy) because of the number of borderline lipid measurements results (col. 16 lines 48-62). It is respectfully submitted that using an NMR subclass profile, such as that disclosed by Otvos, is a means for identifying patient who do not have hyperlipidemia but are in need of treatment (i.e., patients who would ordinarily be overlooked). The motivation being to improve the health care of

patients by using the subclass information as a more reliable indicator of a patient's risk to develop coronary heart disease (col. 1 line 42 to col. 2 line 11).

Krauss discloses using segmented gradient gel electrophoresis to determine the subclasses of LDL particles and HDL particles (col. 1 line 15 to col. 2 line 47, col. 14 line 61 to col. 16 line 22).

Claim 23 is rejected as obvious over Levin, Otvos and Krauss and in further view of U.S. Patent 6,024,699 Surwit. The Patent Office applies Surwit as follows:

Surwit discloses a system for monitoring, diagnosing, prioritizing, and treating chronic medical conditions of a plurality of remotely located patients, wherein treatment information is provided to a patient via a computer network (Fig. 1 and 3, col. 2 lines 38-55, col. 3 lines 24-38, col. 6 line 27 to col. 7 line 13, col. 9 lines 24-58, col. 18 line 45 to col. 19 line 40).

VII. Argument

It is first noted that the claimed invention differs significantly from the cited references Levin, Otvos and Krause as follows:

Levin U.S. Patent 5,724,580

The Office Action acknowledged that Levin does not disclose a data base with LDL subclasses and HDL subclasses. Levin does not recognize the LDL subclass and HDL subclass analysis can identify patients that have apparently normal LDL and HDL total values, which the whole point of the invention. Applicant's healthcare management system achieves this important health care advancement which was not known to exist in the prior art nor was it predictable. The expanded data unpredictability revealed the claimed relationship. Such a data base does not exist in the art and the results derived from such a data base are not obvious because it could not be determined if the claimed result even existed until applicant collected and analyzed the data

base. Such a retrospective look at applicant's results and specification can not be the basis for obviousness. If anything Levin teaches away from applicants invention in that it only considers total HDL and LDL in the data base. For example, figure 25A of Levin provides:

> LIPID PROFILE
>
> > Our records do not include any data on the lipid levels of patient. Since lipids are a major modifiable risk factor for CAD and its complications, we recommend obtaining LDL, HDL and triglyceride levels before the patient's next ischemia monitoring with Monitor One STRx. If these values are currently known, please report them to us.

Applicants claim a system that determines cardiovascular disease where total HDL and total LDL are normal. Levin does not suggest LDL subclass and HDL subclass data base and does not suggest the claimed result. There is no suggestion to combine Levin with information found in Otvos and Krause.

Otvos U.S. Patent 6,576,471

Otvos describes determining some HDL and LDL subclasses by NMR. The limitation of NMR are described in the Shewmake Declaration in the Response of December 27, 2004. Thus NMR is not capable of accurately determining key subclasses such as HDL 2b. Otvos does not recognize the possibility of identifying patients with normal LDL and HDL who need treatment and the NMR technique is incapable of doing so. We note the applicant's claims are limited to gradient gel electrophoresis data for respective HDL and LDL subclass data and HDL 2b is a required subclass.

Krauss U.S. Patent 5,925,229

Krauss only describes the use of segmented gel electrophoresis to determine some LDL subclasses and does not describe the separation of HDL subclass. Krauss does not describe a data base of LDL subclasses or HDL subclasses. Krauss does not describe any HDL subclasses,

much less the HDL 2b subclass present in the data base of the claimed health care management system.

In order for a combination of references to render an invention obvious, it must be obvious that their teachings can be combined. In re Avery (CCPA 1975) 518 F2d 1228, 186 USPQ 161. Obviousness cannot be established by combining the teaching of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. In re Geiger (CAFC 1987) 815 F2d 686, 2 PQ2d 1276; In re Fine (CAFC 1988) 837 F2d 1071, 5 PQ2d 1596. The mere fact that references can be combined does not render the resultant combination obvious unless the prior art also suggest the desirability of the combination, Berghauser v. Dann, Comr. Pats. (DCDC 1979) 204 uSPQ 393; ACS Hospital Systems, Inc. v. Montefiore Hospital (CAFC 1984) 732 F2d 1572, 221 USPQ 929. References which merely indicate that isolated elements and/or features recited in the claims are known is not a sufficient basis for concluding that the combination of claimed elements would have been obvious. In the present case, the references do not suggest the claimed element, as pointed out above. Ex Parte Hiyamizu (BPAI 1988) 10 PQ2d 1393. Where the references expressly teach away from what the PTO contends is obvious from the references, there is no basis for combination, In re Grasseli et al, (CAFC 1983) 713 F2d 731, 218 USPQ 769. The references, viewed by themselves and not in retrospect, must suggest doing what applicant has done. In re Shaffer (CCPA 1956) 229 F2d 476, 108 USPQ 326, In re Skoll (CCPA 1975) 523 F2d 1392, 187 USPQ 481.

To properly combine references to reach a conclusion of obviousness, there must be some teaching, suggestion or inference in the references, or knowledge generally available to one of ordinary skill in the art, which would have led one to combine the relevant teaching of the two references. Ashland Oil Inc. v. Delta Resins and Refractories, Inc., et al. (CAFC 1985) 776 F2d 281, 227 USPQ 657; 5 PQ2d 1532. Both the suggestion to make the claimed process and the reasonable expectation of success must be founded in the prior art, not in applicant's disclosure. In re Vaeck (CAFC 1991) 20 USPQ 1938.

There is no suggestion to combine Levin, Otvos and Krauss to provide a healthcare management system for identifying patients who do not have hyperlipidemia based on total LDL cholesterol and total HDL cholesterol, but are in need of treatment. Indeed the combination of Levin, Otvos, and Krauss does not produce the claimed invention because the necessary data base is not present in the references whether taken alone or in combination.

35 U.S.C. § 103(a) provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title [35 USC 102], if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.,* 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The above references and related discussion is representative of the prior art as a whole. The difference of the claimed invention and the prior art is illustrated by considering the only independent claim, claim 38 as it relates to the prior art as a whole.

38. A cardiovascular healthcare management system comprising:

(a) an infomediary site having databases for cardiovascular healthcare management which includes a database of test results of concentration of subclasses of LDL particles and subclasses of HDL particles from at least 900 cardiovascular patients;

(b) a data entry interface for receiving patient personal data and test results for concentration of subclasses of LDL particles and subclasses of HDL particles storing the data and results in the infomediary site databases;

(c) a diagnostic engine for analyzing patient test results for subclasses of LDL particles, subclasses of HDL particles data and identifying patients who do not have hyperlipidemia based on total LDL cholesterol and total HDL cholesterol, but are in need of treatment; and

(d) wherein the subclasses of LDL particles and subclasses of HDL particles are levels determined by segmented gradient gel eletrophoresis and wherein the particle sub-classes include HDL 2b.

Claim 38 differs from the prior art in that claim 38 utilizes a 900 cardiovascular patient data base of LDL subclasses and HDL subclasses to identify patients with normal total HDL and LDL levels who are in need of treatment based on the LDL and HDL subclass data base where HLD 2b is an essential subclass in the data base.

There is no suggestion in the prior art that such a relationship could exist and no way of predicting or determining that patients with normal total HDL and LDL would require treatment based on HDL or LDL subclass data prior to applicants 900 patient data base which permitted the

analysis and permitted the identification of patients with normal HDL and LDL that needed treatment. There is no suggestion that HDL 2b subclass is essential to the success of the data base in identifying patients with normal HDL and LDL who are in need of treatment. Thus it is applicants' objective data and the result from the analysis of that data that provides the claimed invention. One of ordinary skill in the art did not have the database, the results of the database, and could not have known or predicted the results.

Since claims 22, 23 and 24-28 are dependant on claim 38, the above arguments are equally applicable to the nonobviousness of the dependant claims. The limitation of claim 23 is not relied on for patentability. Therefore, the Surwit 6,024,699 patent cited in the Office Action relates only to claim 23 is not discussed.

Conclusion

Claims 38 and 22, 24-28 dependant thereon are not obvious in view of the prior art. Claim 23 also dependant on claim 38 is also not obvious in view of the prior art.

Respectfully submitted,

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP

Date: April 11, 07

By: _____

John J. McDonnell
Reg. No. 26,949

CLAIMS APPENDIX

1. (Canceled)
2. (Canceled)
3. (Canceled)
4. (Canceled)
5. (Canceled)
6. (Canceled)
7. (Canceled)
8. (Canceled)
9. (Canceled)
10. (Canceled)
11. (Canceled)
12. (Canceled)
13. (Canceled)
14. (Canceled)
15. (Canceled)
16. (Canceled)
17. (Canceled)
18. (Canceled)
19. (Canceled)
20. (Canceled)
21. (Canceled)

22. (Previously Presented) The cardiovascular healthcare management system of claim 38 further comprising a physician data access interface to allow physician access to the infomediary databases.

23. (Previously Presented) The cardiovascular healthcare management system of claim 38 further comprising a communication system allowing the physician to communicate cardiovascular healthcare management information to the patient.

24. (Previously Presented) The cardiovascular healthcare management system of claim 38 further comprising a cardiovascular knowledge base that stores information related to cardiovascular risk factors.

25. (Previously Presented) The cardiovascular healthcare management system of claim 38 wherein the diagnostic engine includes algorithms for associating test results with possible treatments.

26. (Previously Presented) The cardiovascular healthcare management system of claim 38 wherein the diagnostic engine includes algorithms for associating test results with possible diagnoses.

27. (Previously Presented) The cardiovascular healthcare management system of claim 38 wherein the diagnostic engine includes algorithms for associating diagnosis information with possible treatment plans.

28. (Previously Presented) The cardiovascular healthcare management system of claim 27 wherein the treatment plans include personalized drugs, diet and exercise suggestions.

29. (Canceled)

30. (Canceled)

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. (Canceled)

37. (Canceled)

38. (Previously Presented) A cardiovascular healthcare management system comprising:

(a) an infomediary site having databases for cardiovascular healthcare management which includes a database of test results of concentration of subclasses of LDL particles and subclasses of HDL particles from at least 900 cardiovascular patients;

(b) a data entry interface for receiving patient personal data and test results for concentration of subclasses of LDL particles and subclasses of HDL particles storing the data and results in the infomediary site databases;

(c) a diagnostic engine for analyzing patient test results for subclasses of LDL particles, subclasses of HDL particles data and identifying patients who do not have hyperlipidemia based on total LDL cholesterol and total HDL cholesterol, but are in need of treatment; and

(d) wherein the subclasses of LDL particles and subclasses of HDL particles are levels determined by segmented gradient gel eletrophoresis and wherein the particle sub-classes include HDL 2b.

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RELATED PROCEEDINGS APPENDIX

None

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EVIDENCE APPENDIX

1. U.S. Patent 5,724,580 (Levin)
2. U.S. Patent 6,576,471 (Otvos)
3. U.S. Patent 5,925,229 (Krauss)
4. U.S. Patent 6,024,699 (Surwit)
5. Declaration of David T. Shewmake

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Filed: March 24, 2000	)	
	)	
Title: CARDIOVASCULAR HEALTHCARE MANAGEMENT SYSTEM AND METHOD	)	

RULE 132 DECLARATION OF DAVID T. SHEWMAKE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, David T. Shewmake, declare and state as follows:

1. I am an inventor of the above-identified application.

2. I am familiar with analysis of the Berkeley HeartLab data related to LDL IIIa and IIIb and HDL 2b as it relates to subjects with normal LDLC and HDLC and the need for medical treatment.

3. I submitted a Declaration with regard to a related case, Serial No. 10/122,081.

4. The data base relating to LDL subclasses and HDL subclasses is not a publicly available data base. This data base was accumulated at Berkeley HeartLab. At the time the application was filed, there were approximately 954 subjects in the data base. There are now approximately 209,000.

5. I have reviewed U.S. Patent 6,576,471 B2 (Otvos), (Exhibit B). Otvos describes a method for determining 2 subsets of lipid particles by NMR. The method of Otvos described in that patent is not capable of determining in excess of 40% of subjects with normal HDL and LDL levels who are in need of treatment based on subparticle analysis described and claimed in the above-application and which uses a next generation and thus more discriminating technology, "segmented gradient gel electrophoresis". For Berkeley HeartLab there exist two different segmented gel configurations: one for LDL-S3-GGE (3 distinct discontinuous segments) and another for HDL–S10-GGE (10 distinct discontinuous segments). The differentiation of result achieved from the "segmented gradient gel electrophoresis" when compared to the NMR. was described in the presentation entitled **Comparison of Traditional and Alternative Laboratory Methods for the Determination of Lipid Measurements, Lp(a) and LDL Subclass Patterns** as presented at the American Heart Association (AHA) 42nd Annual Conference on Cardiovascular Disease Epidemiology and Prevention, April, 2003 (Exhibit C). The following observations and analyses from this presentation are concluded:

A. NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 7 subclasses of LDL; NMR essentially reports 2 subclasses: Pattern A and Pattern B. Without the 7 subclass discrimination, certain patient samples are misclassified as large LDL molecules "no treatment needed", when in fact they would have been "treatment recommended" i.e., small dense samples if more stringent or "granular" analysis were utilized. This "false negative" treatment conclusion constitutes the essence of the database difference which imposes a significantly varied and more relevant clinical conclusion when using the Berkeley HeartLab database.

B. NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 5 subclassses of HDL; NMR only reports 2 subclasses of HDL: large and small. Within the 5 subclass discrimination, the most significant as an indicator of the status of "reverse cholesterol transport" is HDL 2b. NMR can not accurately discriminate and reproducibly analyze HDL 2b. Without the HDL 2b discrimination, certain patient samples are misclassified as "no treatment needed", when in fact they would have been "treatment recommended" if the more stringent or "granular" analysis of HDL 2b were available and utilized. This "false negative" treatment conclusion constitutes the essence of the database difference with respect to HDL and impaired reverse cholesterol transport. This technology difference imposes a significantly varied and a more relevant clinical conclusion within the Berkeley HeartLab database when compared to NMR.

C. The NMR technology has never been correlated to the gold standard AnUC (analytical ultracentrifugation) method for describing lipoprotein subclasses. AnUC and the "segmented gradient gel electrophoresis" describe a correlated result for the 7 subclassses of LDL; NMR only reports essentially 2 subclasses of LDL: Pattern A or Pattern B. Within the 7 subclass discrimination, the smallest of the subclasses and the most significant as both an indicator of treatment degree of aggressiveness as well as a guide for immediacy of response is LDL IVb. A number of papers and abstracts have been published in the last few years supporting this position. NMR can not accurately discriminate or reproducibly analyze LDL IVb. Without the LDL IVb discrimination, certain patient samples would be either misclassified as "no treatment

needed", instead of "treatment recommended" if the more stringent or "granular" analysis of LDL IVb were available and utilized or would have improper treatment plans resulting in extended treatment, compromised outcomes and/or improper longitudinal clinical data. This "false negative" or degree of aggressiveness treatment conclusion constitutes the essence of the database difference with respect to LDL. This technology difference imposes a significantly varied and a more relevant clinical conclusion within the Berkeley HeartLab database when compared to NMR.

D. In reading through the Otvos patent (Exhibit B) there is no reference to mischaracterizing patients as being healthy compared to NCEP (National Cholesterol Education Program) ATP III guidelines when in fact those patients are in need of treatment. This is the point of our patent application that we discovered with our segmented gradient gel technology and our Berkeley HeartLab database. There does not seem to be a conflict between the Otvos patent and our patent application in terms of mischaracterizing patients as the Otvos patent does not make this comparison to ATP III or address this issue.

E. The Otvos NMR technology described in the 6,576,471 patent is not capable of identifying those patients with normal HDL and LDL who are in need of treatment as described and claimed in this application.

6. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March 23, 2005
Date

David T. Shewmake
David T. Shewmake, Ph.D.